REMARKS

Rejections Under 35 U.S.C. § 103(a)

Claims 1-5, 8-17, 19-21, 29-30, 35-39 and 42 stand rejected under 35 U.S.C. § 103(a) as obvious over Malone[1] in view of Barchfield,[2] as evidenced by Rappuoli.[3]

Applicants respectfully traverse the rejection.

A statement that modifications of the prior art to meet the claimed invention would have been well within the ordinary skill of the art at the time the claimed invention was made is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (B.P.A.I 1993). While there need not be an explicit teaching, suggestion, or motivation to modify prior art teachings, the Patent Office must set forth an "explicit" analysis containing "articulated reasoning." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007).

The Office Action does not make a *prima facie* case that claims 1-5, 8-17, 19-21, 29-30, 35-39, and 42 are obvious because it does not articulate any reason why a skilled artisan would, in view of the prior art, have arrived at Applicants' claimed subject matter.

Malone teaches administering polynucleotides to mucosal membranes to obtain a mucosal immune response. Malone also teaches that the polynucleotides may be delivered by alphaviral vectors and that antigens encoded by the polynucleotides can be derived from sexually transmitted viruses such as HIV. As the Office Action acknowledges at page 5, however, Malone does not teach administering a detoxified bacterial ADP-ribosylation factor. The Office Action asserts that Malone "does teach the

[1] Malone *et al.*, U.S. Patent No. 6110898
[2] Barchfeld *et al.*, WO 98/42375.
[3] Rappuoli, WO 95/17211.

use of adjuvants with his replication defective gene delivery vehicle." Office Action at page 5 citing Malone at col. 3, line 61 to col. 4, line 3. However, the cited section does not teach or suggest using ADP-ribosylating toxins adjuvant in protein form. Rather, it teaches that DNA encoding ADP-ribosylating toxins can be incorporated into the vector:

> The vector may contain a gene encoding an adjuvant, such as the cholera toxin B subunit, to enhance the immunostimulatory effect of the vaccine. In addition to cholera toxin, other natural compounds with mucosal adjuvant properties are streptococcal antigen, and the heat labile toxin (LT) of *E. coli*.

Malone, col. 3, line 65 to col. 4, line 3. Nor is there any other teaching or suggestion in Malone to include ADP-ribosylating toxin in protein form, let alone a detoxified protein version of an ADP-ribosylating toxin. Thus, there is nothing in Malone that suggests that Malone's DNA-based vaccine approach could or should be combined with a detoxified ADP-ribosylating toxin adjuvant. In fact, Malone teaches away from using the toxins in protein form. Malone knew that ADP-ribosylating toxins functioned as mucosal adjuvants; however, he suggests using them only as nucleotide sequences in DNA vaccines to be expressed simultaneously with any other protein encoded by the vaccine.

Neither Barchfeld nor Rappuoli cures Malone's deficiency. Barchfeld teaches detoxified ADP-ribosylating toxins. Rappuoli teaches that the detoxified ADP-ribosylating toxins are effective as mucosal adjuvants. Neither reference teaches or suggests combining detoxified ADP-ribosylating toxin with a replication-defective gene delivery vehicle comprising a polynucleotide encoding at least one antigen.

Claims 1 and 41 stand rejected under 35 U.S.C. § 103(a) as obvious over Malone, in view of Barchfeld, as evidenced by Rappuoli, in further view of McCluskie.[4]

Applicants respectfully traverse the rejection.

McCluskie is cited as teaching the addition of a CpG oligonucleotide. Office Action at page 7. McCluskie teaches using CpG oligonucleotides as a mucosal adjuvant, both alone and combined with cholera toxin. However, McCluskie does not teach or suggest administering detoxified ADP-ribosylating factor mutants with a replication-defective gene delivery vehicle comprising a polynucleotide encoding at least one antigen. McCluskie therefore does not cure the deficiencies of Malone described above. None of the references alone or in combination provide any reason to arrive at Applicants' claimed subject matter. The Office Action has not made a *prima facie* case that claims 1 and 41 are obvious.

Applicants therefore respectfully request withdrawal of the rejection.

Respectfully submitted,
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[4] McCluskie *et al.*, "Cutting Edge: Cpg DNA is a potent enhancer of systemic and mucosal immune responses against hepatitis B surface antigen with intranasal administration to mice." J. Immunol. 1998 161:4463-4466.